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REVIEW

Evidence supporting primary prevention of cardiovascular diseases with statins: Gaps between updated clinical results and actual practice



Preuves à l'appui des statines en prévention primaire des maladies cardiovasculaires : écarts entre les études cliniques et la pratique réelle

Eric Bruckert^a, Jean Ferrières^{b,*}

^a *Department of Endocrinology and Metabolism, Groupe Hospitalier Pitié-Salpêtrière, AP-HP, 47-83, boulevard de l'Hôpital, 75651 Paris cedex 13, France*

^b *Department of Cardiology, Toulouse Rangueil University Hospital, 1, avenue du Professeur-Jean-Poulhès, TSA 50032, 31059 Toulouse cedex 9, France*

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Summary The use of pharmacological lipid-lowering intervention in individuals with hypercholesterolaemia and known cardiovascular disease or diabetes/chronic kidney disease is well established. Current European Society of Cardiology guidelines recommend immediate initiation of drugs in adjunct to lifestyle intervention in these patients at high or very high cardiovascular risk. In these clinical settings, statins are generally chosen as the first-choice drug intervention, in consideration of the robust evidence showing a reduction in all-cause mortality and major adverse cardiac events (MACE). In contrast, primary prevention with statins, even in the subset of patients at high-risk of cardiovascular events, is not well implemented. This might be related to a lack of public awareness regarding the actual risk associated with prolonged exposure to high concentrations of low-density lipoprotein cholesterol (LDL-C) and uncertainties in the clinical evidence coming from the earliest trials in this patient subset. However, recent observational studies suggest that lowering LDL-C earlier in life and for a longer duration can

Abbreviations: ACS, Acute coronary syndrome; CI, Confidence interval; CHD, Coronary heart disease; CKD, Chronic kidney disease; CVD, Cardiovascular disease; HBP, High blood pressure; LDL, Low-density lipoprotein; LDL-C, Low-density lipoprotein cholesterol; MACE, Major adverse cardiac events; NNH, Number needed to harm; NNT, Number needed to treat; OR, Odds ratio; PCSK9, Proprotein convertase subtilisin/kexin type 9; RCT, Randomized clinical trial; RR, Relative risk; RRR, Relative risk reduction.

* Corresponding author.

E-mail address: jean.ferrieres@univ-tlse3.fr (J. Ferrières).

MOTS CLÉS

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HTA

substantially decrease the burden of cardiovascular disease and mortality. Moreover, results from recent well-conducted large meta-analyses of randomized clinical trials showed that primary prevention with statins reduced all-cause mortality by 14% and MACE by > 20% – findings similar to those observed for the use of statins in secondary prevention. Recently published American Heart Association/American College of Cardiology guidelines on the treatment of blood cholesterol emphasize that primary prevention using high-dose statins in individuals with LDL-C \geq 190 mg/dL induces a benefit in atherosclerotic cardiovascular risk reduction that clearly exceeds the potential for adverse effects. We aim in this review to discuss the new data that advocate the use of statins in primary prevention earlier and more frequently, putting the efficacy evidence into perspective with new insights in terms of safety issues.

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Résumé Le recours à un traitement médicamenteux hypolipémiant chez des individus présentant une hypercholestérolémie et une pathologie cardiovasculaire connue (CVD) ou un diabète ou encore une maladie rénale chronique (MRC) est bien établi. Les recommandations actuelles de l'ESC préconisent l'initiation immédiate d'un traitement médicamenteux en complément d'une intervention relative au mode de vie, chez ces patients à haut risque ou très haut risque cardiovasculaire. Dans ces contextes cliniques, les statines sont en général considérées comme le traitement de première intention sur la base de données montrant une réduction de la mortalité toutes causes confondues et des événements cardiovasculaires majeurs (MACE). En revanche, la prévention primaire par les statines, même dans le sous-groupe de patients à haut risque d'événements cardiovasculaires, n'est pas bien appliquée. Ceci pourrait être lié à un manque de sensibilisation du public en ce qui concerne le risque réel associé à une exposition prolongée à un taux élevé de cholestérol lié aux lipoprotéines de faible densité (LDL-C) et aux incertitudes dans la validité des preuves cliniques émanant des premiers essais dans ce sous-groupe de patients. Cependant, des études observationnelles récentes suggèrent que la diminution du taux de LDL-C à un âge précoce et sur une durée plus longue peut diminuer de façon notable l'impact des maladies cardiovasculaires et la mortalité. Par ailleurs, les résultats issus de méta-analyses récentes et rigoureuses, conduites à grande échelle à partir d'essais cliniques randomisés, ont montré que la prévention primaire par des statines réduit la mortalité toutes causes confondues de 14% et les MACE de plus de 20%, soit des proportions comparables à celles observées lors de l'utilisation des statines en prévention secondaire. Les recommandations AHA/ACC publiées récemment sur la prise en charge de l'hypercholestérolémie soulignent le fait que la prévention primaire par de fortes doses de statines chez des individus avec un LDL-C \geq 190 mg/dL induit un bénéfice dans la réduction du risque cardiovasculaire athérosclérotique qui excède clairement le risque de survenue d'événements indésirables. Le but de cette revue est de faire état des nouvelles données qui plaident en faveur de l'utilisation des statines en prévention primaire, de manière plus précoce et plus fréquente que celle appliquée actuellement, en mettant en perspective les preuves d'efficacité et les nouvelles données relatives à la tolérance.

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Introduction

Ischaemic heart disease and stroke were the leading causes of death in 2010, with a relative increase in rates compared with 1990 of 35% and 26%, respectively, and they are still ranked the first and second causes of death worldwide; this represents approximately one in four deaths worldwide for the two diseases combined [1].

When focusing on western countries, such as the USA, an opposite trend is observed, with declining rates of death attributable to cardiovascular diseases (CVDs) in the past decade [2], although they still account for one in every three deaths in the USA. In Europe, the same trends are noted, with deaths due to cardiovascular disease and coronary heart disease (CHD), accounting for 46% and 20% of deaths, respectively, although there are

substantial inequalities between countries [3]. In parallel, we have observed a decline in the prevalence of some modifiable risk factors, such as cigarette smoking rate, uncontrolled high blood pressure (HBP) and average low-density lipoprotein cholesterol (LDL-C) concentration in the population, concurrent with improvements in lifestyle and pharmacological interventions. For instance, regarding HBP control, when comparing data from the 1988–1994 National Health and Nutrition Examination Survey in the USA [4] and the 2007–2008 period, awareness improved from 69.1% to 80.7%, the use of anti-hypertensive drugs increased from 54.0% to 73.5% and the ratio of controlled/treated HBP rates improved from 50.6% to 72.3% [5]. In addition, nowadays, most higher risk patients with HBP and co-morbidities receive anti-hypertensive agents (88.3% use in HBP with chronic kidney disease [CKD], 93.4% use in concomitant

diabetes and 94.0% use in patients with CVD in 2010); these rates are higher than for HBP without co-morbidities (67.8%) [6]. Regarding the LDL-C rate, interesting recent data from the French MONICA registry show that treatment with statins in primary prevention is able to change the initial presentation of acute coronary syndrome (ACS), with more non-ST-segment elevation myocardial infarction and unstable angina and less ST-segment elevation myocardial infarction [7] in comparison with patients not treated with statins before the first manifestation of acute CHD. The objectives of this review are to summarize the clinical research data supporting primary prevention with statins and to analyse gaps in actual practice.

Why focus on primary prevention with statins in high-risk groups?

In contrast to the marked improvement in HBP awareness and treatment rates in high-risk patients, the adoption of lipid-lowering drugs seems to lag behind in a substantial proportion of patients with hypercholesterolaemia and co-morbidities. In the USA, in patients with diabetes, approximately 60% do not receive a lipid-lowering agent [8], and in patients with CKD, fewer than one third receive lipid-lowering drugs and only 40% are at LDL-C goal [9].

In Europe, we observed encouraging trends towards a decrease in mean LDL-C concentrations [10–12], but we also noticed that LDL-C management was worryingly suboptimal in high-risk groups. For instance, in the French MONA LISA study [13], only 42% of patients at high- or very high-risk, according to the latest European guidelines [14], received lipid-lowering therapy. Although a slight majority of patients at very high-risk (58%) actually benefit from a lipid-lowering agent, the vast majority (72%) of those eligible for primary prevention (high-risk group with multiple co-morbidities but no CVD) are excluded from the recommended therapy [13].

We also observed in a large European Union/Canadian registry [15,16] that the low-density lipoprotein (LDL) control rate was not correlated to the actual risk level. The control rate averaged approximately 50% in all patients, varying slightly from 44% in patients with low European Society of Cardiology scores to 58% in very high-risk CVD patients (Table 1) [16].

In France, results from a study conducted in a more specific population of patients aged >45 years who had been treated with statins for >3 months, the control rate was worse in the higher risk group (52% not at goal) compared

with in the overall population of statin users (38% not at goal) [17].

Overall, the key findings of these observational studies suggest that the management of high LDL-C is particularly limited in highest risk groups eligible for primary prevention compared with in those treated for secondary prevention and lower-risk groups.

What is the indirect evidence in favour of earlier initiation and prolonged LDL-lowering interventions?

In a recently published meta-analysis of 312,321 subjects, the researchers used a Mendelian randomization approach to estimate the clinical benefit of lowering LDL early in life. The authors used, as a proxy for a treatment that would decrease LDL-C beginning at birth, the inherited allocation to protective genotypes (for nine single nucleotide polymorphisms associated with lower LDL-C). Results showed that a low LDL-C concentration following this random natural allocation decreases the risk of CHD by 54.5% for each mmol/L decrease in LDL-C. Comparatively, for the same level of LDL-C decrease, statin therapy started later in life would “only” reduce the risk of CHD by 24.0% (Fig. 1) [18]. The authors concluded that long-term exposure to a protective lower LDL-C beginning early in life was associated with a greater reduction in the risk of CHD than the current practice of starting to lower LDL-C later in life.

Mirroring these results, the deleterious effect of early and long-term exposure to dyslipidaemia was studied in the Coronary Artery Risk Development in Young Adults (CARDIA) study [19]. The effect of time-averaged cumulative exposure to dyslipidaemia starting in young adulthood (healthy subjects at enrolment, aged 18–30 years) was assessed over a 20-year period and related to coronary calcium levels measured later in life (estimation based on computed tomography scan by analysts blinded to participant characteristics). Among the 3258 participants, 65% of patients were exposed to LDL-C concentrations >100 mg/dL. The result showed that exposure to high LDL-C concentrations was strongly associated with coronary calcium later in life. Compared with in subjects with optimal LDL-C concentrations <70 mg/dL, the risk of coronary calcium in subjects exposed to slightly suboptimal LDL-C (between 70–99 mg/dL) was 1.5 times higher, although not significantly different (95% confidence interval [CI] 0.7–3.3).

Table 1 Proportion of patients^a whose lipid concentrations were not at goal or abnormal, data from [16].

	All (n = 21,797)	High-risk patients (n = 17,583)	Diabetes (n = 4524)	CVD (n = 10,587)	ESC score < 5% (n = 4214)
TC not at goal (%)	54.4	52.1	51.9	46.5	63.9
LDL-C not at goal (%)	48.5	46.8	45.3	41.9	55.8

CVD: cardiovascular disease; ESC: European Society of Cardiology; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol.

^a Patients were recruited from 2954 treatment centres in 11 European Union countries (Norway, Sweden, Denmark, Netherlands, Germany, Austria, Ireland, United Kingdom, France, Portugal and Spain) and Canada.

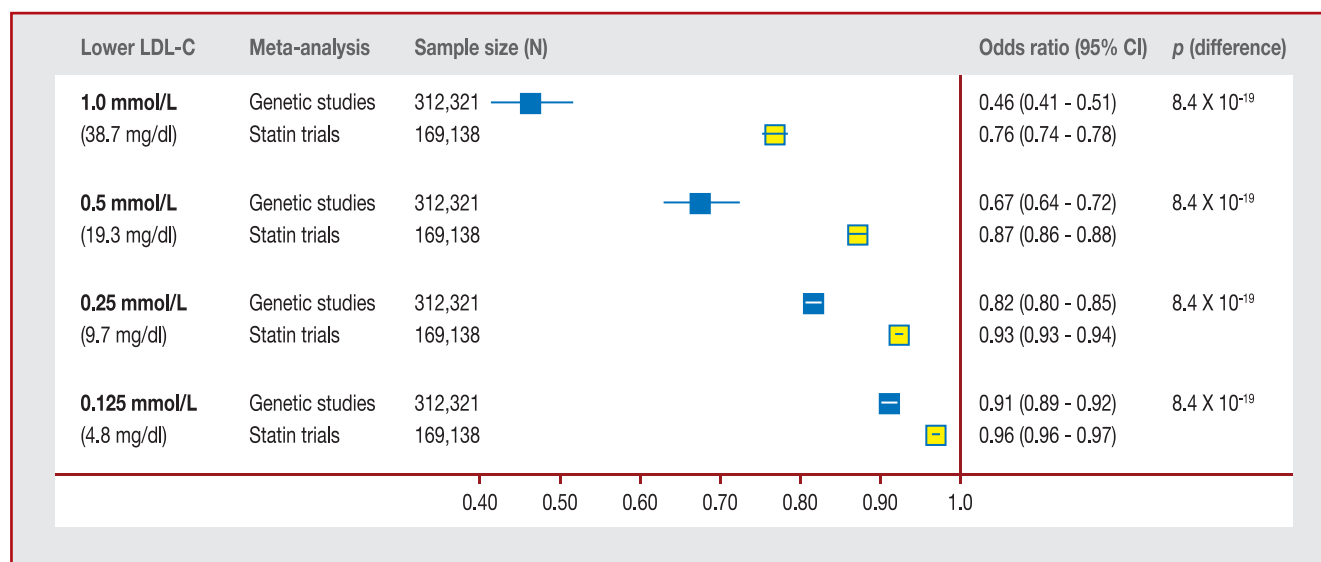


Figure 1. Comparative coronary heart disease risk reduction of earlier and later low-density lipoprotein cholesterol (LDL-C) lowering. CI: confidence interval; OR: odds ratio. Reproduced with permission from [18].

Nevertheless, subjects with concentrations even marginally higher (100–129 mg/dL) had an amazing 2.4 times higher risk of coronary calcium (odds ratio [OR] 2.4, 95% CI 1.1–5.3) and those with concentrations ≥ 160 mg/dL had a 5.6 times higher risk (OR 5.6, 95% CI 2.0–16).

This indirect evidence supports the paradigm of earlier and longer duration of high LDL-C management and suggests a need for earlier screening and improved identification of patients who would be eligible for pharmacological intervention. Regarding the pharmacological management of patients with high LDL-C, the recently published “American Heart Association/American College of Cardiology guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults” are very specific. Adults aged ≥ 21 years with primary LDL-C ≥ 190 mg/dL should be treated with statin therapy using a high dosage unless contraindicated [20].

What is the direct evidence for benefit and risk of primary prevention with statins?

The Cochrane Collaboration is a non-profit organization founded in 1993, consisting of an international group of close to 30,000 researchers from more than 100 countries that aims to independently review and analyse medical information in the interests of evidence-based medicine and public health. Since 2011, the collaboration has developed, as a non-governmental organization, an official partnership with the World Health Organization, with a seat on the World Health Assembly to provide input into World Health Organization resolutions [22,23].

In the most recently published Cochrane systematic review and meta-analysis of randomized clinical trials (RCTs), Taylor et al. concluded that the evidence showed that primary prevention with statins was likely to be cost-effective and may also improve patient quality of life [21].

Two years earlier, the same authors had argued the opposite position, contending that the evidence did not advocate routine implementation of primary prevention with regard to cost-effectiveness, although a reduction in all-cause mortality and composite cardiovascular events was already observed in this 2011 meta-analysis; they expressed concerns about the interpretation of the results due to possible under-reports of outcomes and adverse events and the inclusion of some patients with a history of CVD [24]. What changed between the two publications was the arrival of new evidence from RCTs, enlarging the clinical data set from 34,000 patients/14 RCTs in the 2011 meta-analysis to 57,000 patients/18 RCTs in the 2013 review.

What has this new clinical evidence taught us? The most important finding is that primary prevention with statins significantly reduces all-cause mortality by 14% (OR 0.86, 95% CI 0.79–0.94); it also decreases the risk of fatal and non-fatal CVD by approximately 20–25% (relative risk [RR] 0.75, 95% CI 0.70–0.81), the risk of combined fatal and non-fatal CHD events (RR 0.73, 95% CI 0.67–0.80) and the risk of combined fatal and non-fatal strokes (RR 0.78, 95% CI 0.68–0.89). More importantly, in terms of cost-effectiveness, the corresponding number needed to treat (NNT) for 5 years to prevent one event would be fairly low: an NNT of 96 to avoid one death from all causes; an NNT of 56 to prevent one CHD event (fatal or not); an NNT of 35 to avoid one cardiovascular event (fatal or not); and an NNT of only 20 to prevent one stroke (fatal or not).

The work conducted by the Cholesterol Treatment Trialists’ (CTT) Collaborators [25] showed results consistent with and complementary to the analysis performed by the Cochrane collaboration. This very large individual patient data meta-analysis included 27 trials with approximately 175,000 patients with high LDL-C concentrations, which compared statins versus control (22 RCTs) or high-dose versus low-dose statins (5 RCTs). The primary finding in the overall population was that for each 1.0 mmol/L

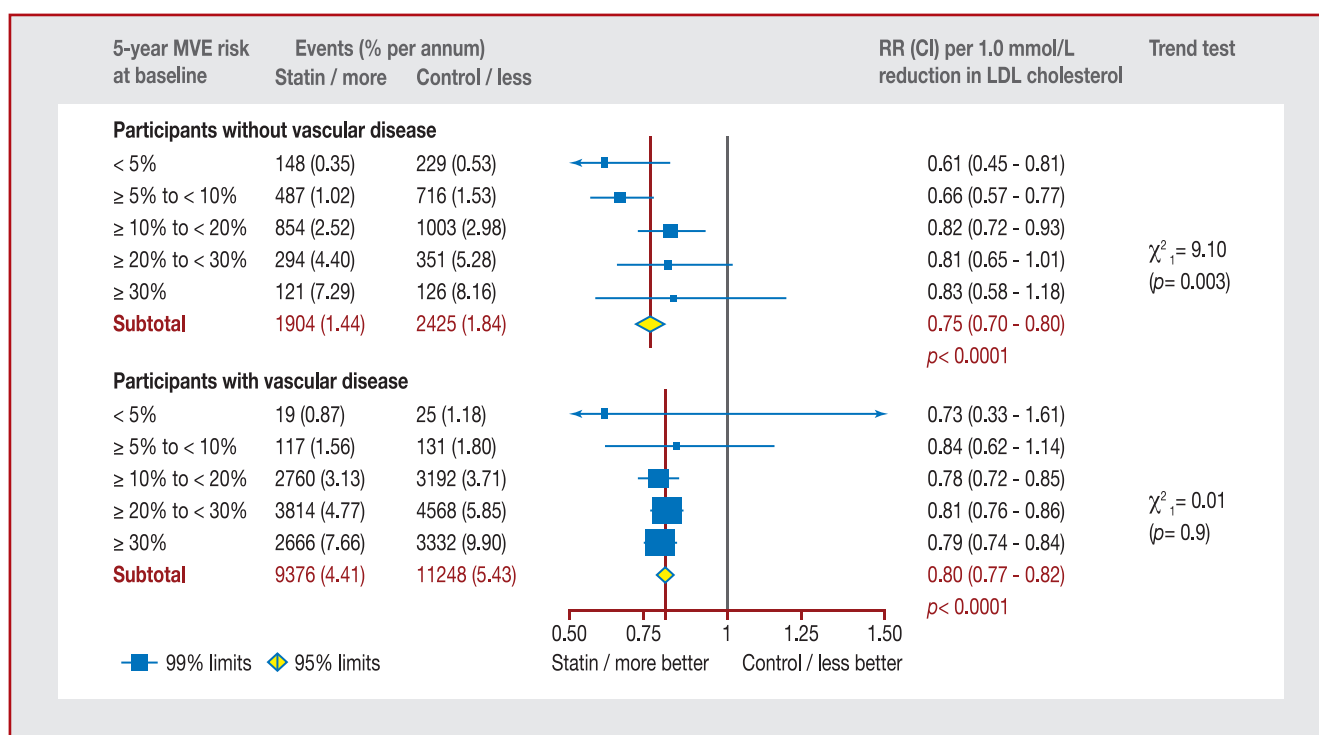


Figure 2. Global effects on major vascular events (MVE) per 1.0 mmol/L reduction in low-density lipoprotein (LDL) cholesterol at different levels of risk, by history of vascular disease. CI: confidence interval; RR: relative risk. Reproduced with permission from [25].

reduction of LDL-C by statin therapy, the risk of major vascular events decreased by 21% (RR 0.79, 95% CI 0.77–0.81, per 1.0 mmol/L). The RR reduction (RRR) for major vascular events was 25% (RR 0.75, 95% CI 0.70–0.80) when statins were used in patients without a previous history of vascular disease, which was similar to the RRR of 20% (RR 0.80, 95% CI 0.77–0.82) achieved for secondary prevention (Fig. 2) [25]. Significant reductions in vascular death by 15% and 12% per 1.0 mmol/L LDL-C decrease were observed in the primary and secondary prevention settings, respectively. This mortality reduction remained significant even after exclusion of patients with diabetes or CKD at baseline. Interestingly, the reduction in major vascular events was also statistically significant in the subset of patients with low estimated cardiovascular risk at baseline (risk < 10% at 5 years).

We therefore have strong evidence coming from large well-conducted meta-analyses that primary prevention with statins is beneficial in reducing MACE, cardiovascular death and all-cause mortality and, owing to the low NNTs observed, that this therapeutic strategy is cost-effective [26].

One should, however, consider the balance between benefit and risk related to statin therapy. In the latest Cochrane meta-analysis, there was no overall difference in the occurrence of all adverse events between the statin and control groups (RR 1.00, 95% CI 0.97–1.03) and no evidence for any serious harm induced by primary prevention with statins, particularly regarding the risk of cancer, haemorrhagic stroke and rhabdomyolysis. However, a significantly higher rate of diabetes was observed in the active treatment arm versus control (RR 1.18, 95% CI 1.01–1.39); this corresponded to an absolute risk increase of 0.4% (2.8% for statins

compared with 2.4% in the control and placebo arms, respectively), which would correspond to a number needed to harm (NNH) of 250 patients treated with statins over 5 years to induce one case of diabetes. Similar findings were observed in an earlier meta-analysis performed among more than 90,000 patients, focusing on incidental diabetes in statin trials [27]. The authors used a conservative pre-specified criterion for defining the incidental diabetes cases: two glucose concentrations ≥ 7.0 mmol/L in trials that measured fasting glucose every 6 months and only one value ≥ 7.0 mmol/L in trials that measured fasting glucose less frequently than 6 months. The risk of incident diabetes was 1.09 times higher with statins (OR 1.09, 95% CI 1.02–1.17), corresponding to an NNH of 255 patients treated for 4 years to induce one extra case of “diabetes” as defined above. We cannot therefore rule out the possibility that statin-treated patients may have an increased likelihood of diabetes, but when translating these results in a clinically meaningful way, we should stress that incidental diabetes as defined in RCTs is only a biological surrogate for possible diabetic long-term complications. In other words, for 250 patients treated over 5 years, one case of hyperglycaemia/diabetes might be due to the statin use, but in parallel, you would avoid at least two deaths and prevent four CHD events and 12 strokes.

Moreover, in patients with documented diabetes at baseline, irrespective of whether the patient has a prior history of vascular disease, statins significantly reduce the risk of myocardial infarction or coronary death, coronary revascularization and the risk of stroke [28].

Regarding other biological abnormalities possibly induced by the use of statins, the Cochrane review suggested

that primary prevention with statins might induce a non-significant trend toward more cases of liver enzyme elevation (RR 1.16, 95% CI 0.87–1.54) but without any increase in the risk of clinically relevant liver dysfunction. However, in a larger meta-analysis (close to 250,000 patients), including trials in primary and secondary prevention, the increased risk of transaminase elevation associated with statins was statistically significant (OR 1.51, 95% CI 1.24–1.84). These results probably reflect the dose-dependent relationship of statins with some specific adverse effects [29].

The dose-dependent relationship is also questioned for statin-induced myotoxicity, ranging from the asymptomatic rise in creatine kinase concentration, myalgia and myositis to the rare but severe rhabdomyolysis. Whereas there was no increase in myalgia in the Cochrane primary prevention meta-analysis (RR 1.03, 95% CI 0.97–1.09), other systematic reviews have suggested that statin type and/or high statin dose (secondary prevention) would increase the risk in creatine kinase elevation and myalgia by up to four times versus control [29,30] and the risk of rhabdomyolysis by three times [31].

This statin-induced myotoxicity not found in primary prevention trials and meta-analyses may, however, have a broader implication for clinical practice than increasing asymptomatic glycaemia elevation. In the non-selected patients in our real-life practice, the incidence of skeletal muscle-related adverse effects is more important than in RCTs [32] and could affect patient adherence to statin therapy, thus, leading to a deleterious effect on the risk of MACE. The observed difference between RCTs and real-life uncontrolled studies is likely to be related to the lower representation in RCTs of patients with factors associated with an increased risk of myopathy (e.g. polypharmacy, concomitant use of fibrates, use of statins above recommended dose, young sporty subjects, etc.) [33]. For instance, one trigger of symptomatic myopathy commonly seen in our clinical practice is abrupt intensive physical activity [34]. Statins were also shown recently to increase exercise-related muscle injury in marathon runners [35].

As for severe chronic muscle toxicity, literature is scarce and review is made even more complex due to the various definitions of “myotoxicity” used by different Health Authorities or academic entities [36]. For example, the US Food and Drug Administration defines myotoxicity as the presence of symptoms of myalgia and creatine kinase > 10 times the upper limit of normal, whereas the American College of Cardiology considers symptoms of myalgia to be sufficient. In addition, the most important barrier that clearly influences the importance of statin-induced severe myotoxicity is the rarity of occurrence. Large cohort studies suggest that the incidence of rhabdomyolysis ranges from 0.44 to 5.4 per 10,000 person-years with statin monotherapy, corresponding to an NNT of 23,000 to induce one case [37]. Another issue is the difficulty in diagnosing and definitely attributing the serious adverse event to the lipid-lowering therapy. For instance, immune myositis (a newly identified entity among chronic statin-induced myopathy) is a rare adverse event with a prevalence not clearly established, and its diagnosis relies on a complex set of clinical, biological and imaging criteria. An immune myositis diagnosis can be suspected in case of muscle weakness/atrophy persisting for weeks or months after statin discontinuation,

biopsy showing a predominantly necrotizing myopathy with minimal lymphocytic infiltrates and positive anti-HMGCR (3-hydroxy-3-methylglutaryl coenzyme A reductase) antibodies [38,39].

Until now, studies have failed to identify genetic variations with large effects on statin efficacy or toxicity. Mangravite et al. recently identified six expression quantitative trait loci that interact with simvastatin exposure and, especially, one locus associated with incidence of statin-induced myotoxicity [40].

What is the benefit of a moderate versus a high-dose of statin started earlier in life in high-risk patients?

High-risk patients include both high-risk and very high-risk patients. According to the European Society of Cardiology/European Atherosclerosis Society guidelines [14], the category of high-risk patients includes subjects with any of the following: markedly elevated single risk factors, such as familial dyslipidaemia and severe hypertension; a calculated SCORE risk $\geq 5\%$ and $< 10\%$ for the 10-year risk of fatal CVD. The category of very high-risk subjects includes patients with any of the following: documented CVD by invasive or non-invasive testing (such as coronary angiography, nuclear imaging, stress echocardiography, carotid plaque on ultrasound); previous myocardial infarction, ACS, coronary revascularization (percutaneous coronary intervention, coronary artery bypass graft) and other arterial revascularization procedures, ischaemic stroke or peripheral arterial disease; type 2 diabetes, type 1 diabetes with target organ damage (such as microalbuminuria); moderate-to-severe CKD (glomerular filtration rate $< 60 \text{ mL/min/1.73 m}^2$); a calculated 10-year SCORE risk $\geq 10\%$. For the SCORE risk, the 10-year risk of fatal CVD in populations at high CVD risk is based on five risk factors (age, sex, smoking, systolic blood pressure and total cholesterol); to convert the risk of fatal CVD to the risk of total (fatal + non-fatal) hard CVD, multiply by 3 in men and 4 in women, and by slightly less in old people.

Lessons from nature-inherited traits that gave rise to lifelong high (familial hypercholesterolaemia) or low (proprotein convertase subtilisin/kexin type 9 [PCSK9] loss of function) LDL concentrations showed that the long-term risks and benefits of varying plasma LDL concentrations may be greater than the intervention trials suggest [41]. The Mendelian randomization studies conducted by Ference et al. [18] and Cohen et al. [42] showed that the benefit of a lifelong low LDL-C concentration, as a result of genetic polymorphisms, was three times higher than that reported in statin trials of only 5–6 years’ duration. Furthermore, a lifelong 39 mg/dL decrease in LDL-C from a PCSK9 mutation was associated with a 54.5% reduction in the risk of CHD. Conversely, a lifelong 34 mg/dL increase in LDL-C doubles the risk of coronary artery disease compared with in patients who develop raised cholesterol in later adult life. Together, these findings suggest that initiation of LDL-lowering throughout life, including in childhood and adolescence, and in the primary prevention setting leads to a greater clinical impact in terms of CVD reduction.

Furthermore, genetically mediated changes in LDL-C are likely to be a better reflection of the cumulative effect of lifelong exposure to differences in circulating LDL-C compared with measurements in adulthood. Although the benefits of lifelong statin therapy appear to be incontrovertible, a question arises regarding the benefit of moderate versus high-doses of statins started earlier in life in high-risk subjects, as there is concern about the tolerability of high-doses of statin, as discussed above.

Several trials have compared more intensive versus standard statin regimens [43,44] to determine whether higher reductions in LDL-C safely lead to further reductions in MACE. Although the results showed a trend in favour of high-dose statin therapy over standard-dose therapy [45], few studies had significant results for their primary outcomes [46,47].

The whole discussion is complex, as we have to take into account the possible side effects with long-term statin treatment (> 5 years) and increased frequency of side effects with high-doses. The fact that there is a continuing debate is illustrated by various guidelines in which high-intensity statins are recommended for some high-risk patients whereas others are advised to start at moderate doses (American College of Cardiology/American Heart Association) [20].

How can we improve primary prevention in high-risk patients?

It has become a priority to increase public and physician awareness of the new evidence demonstrating the benefit of primary prevention with statins. An important necessity is to further explain the clinical benefit relevance in terms of NNT and absolute risk decrease. Indeed, the RRR expressed as a percentage is useful to describe the extent of the efficacy among similar drugs or versus a placebo, but does not reflect the importance of the clinical benefit among the whole arsenal of cardioprotective drugs. Other agents or family of drugs are widely used in the primary prevention of MACE, despite variable levels of evidence and larger NNTs than statins. The use of aspirin is indisputable for the secondary prevention of coronary events but is increasingly debated for primary prevention [48], although its use was reported to reach up to 18% in patients at low cardiovascular risk [49]. For diabetic patients, the American Diabetes Association and the American Heart Association jointly recommended in 2007 that aspirin should be used as a primary prevention strategy in those at high cardiovascular risk [50], but new evidence from inconclusive trials has raised questions about its actual benefit in primary prevention [51,52]. A recent large meta-analysis [53], including the latest primary prevention trials and more than 100,000 patients followed for a mean duration of 6 years, showed that aspirin treatment reduced total cardiovascular events by 10% (NNT=120). Results were driven primarily by a significant reduction in non-fatal myocardial infarction (NNT=162), without a significant reduction in cardiovascular-related death (OR 0.99, 95% CI 0.85–1.15) and at the expense of an increased risk of clinically relevant bleeding events (NNH=73). As for statin therapy, the 2013 Cochrane meta-analysis demonstrated that the corresponding NNTs were 35 to prevent one cardiovascular event and 56 to avoid one total CHD

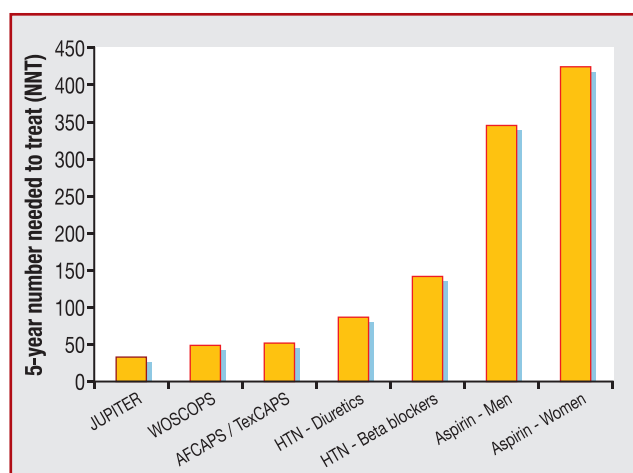


Figure 3. Five-year number needed to treat values to prevent one major cardiovascular event in comparable primary prevention populations for statin therapy, anti-hypertensive therapy and aspirin. Reproduced with permission from [58].

event. As opposed to evidence with aspirin, statins significantly reduced cardiovascular-related death (NNT = 30) and all-cause death (NNT = 96) [21].

These results can also be put in perspective with anti-hypertensive drugs. Diuretic and beta-blocker therapies significantly reduce total cardiovascular events, but the NNTs would be at least twice as high as for statins, with values between 86 for diuretics and 140 for beta-blockers. Network meta-analyses also suggest that the effect size on morbidity and mortality varies markedly with the class of anti-hypertensives. The only agents to have consistently proved reduction in all-cause death (RRR ~10%) in direct or through network comparisons are diuretics [54,55]. In contrast, beta-blockers did not reduce all-cause deaths (RR 0.99, 95% CI 0.88–1.11) or CHD events in a recent Cochrane meta-analysis [56].

Thus, despite explicitly excluding patients with LDL-C > 130 mg/dL and including large numbers of women (who have lower event rates than men), the absolute risk reductions observed in the JUPITER trial [57] and the concomitant NNT values are, if anything, superior to those for statin therapy in the primary prevention of vascular events among hyperlipidaemic men or the prophylactic use of anti-hypertensive or anti-thrombotic therapies among middle-aged and older men and women (Fig. 3) [58].

Finally, the robustness of evidence is highest with statin use in primary prevention compared with any other class of medication routinely prescribed to prevent MACE.

The purpose of the review is not to add confusion to the current controversy about which class of medication should be used for primary prevention of cardiovascular events, but rather to question the reasons why statins are used less frequently than other drugs in patients at risk.

Why is primary prevention in high-risk patients not adequately implemented?

Whatever the type of primary care pharmacological intervention, one commonly debated question before routinely

implementing primary prevention is the pharmaco-economic aspect. One may argue, for example, that statin therapy is expensive and that prescribing it to all high-risk patients would represent an unnecessary financial burden to the public health system. We should, however, consider two dimensions of the pharmaco-economic assessment.

The first dimension is at “patient and disease level”. What is the cost-effectiveness of a given treatment versus a placebo/non-treated control if prescribed to all patients who actually deserved to be treated? The answer to this question relies primarily on RCTs and meta-analyses of trials conducted in this population. If the societal cost induced by the adverse event (e.g. MACE) is higher than the overall treatment cost, and if the drug was proven to be effective in RCTs, there is a good chance that the pharmaco-economic evaluation would favour the prevention strategy over no treatment. The lower the NNT the higher this probability is. We have shown in this example that primary prevention with statins is likely to be cost saving if prescribed to high-risk patients, at least as much as (and probably more than) primary prevention with anti-hypertensives or aspirin (the latter not being cost-effective, with no evidence for efficacy and a low NNH for bleeding).

The second dimension is at the general population level. The pharmaco-economic evaluation is more difficult to conduct and varies according to regional specificities. One should consider the prevalence of the risk factor in the given population (e.g. USA versus European Union), costs related to screening the population, probability that the treatment is given to the appropriate patients, adherence to the prescribed treatment, etc. [59]. Briefly, the epidemiological specificities and real-life local practice/habits become important determinants in assessing the cost-effectiveness of a primary prevention strategy. For instance, in France, the direct cost related to statin prescription is one of the highest among reimbursed drugs, with yearly per-patient costs ranging between 85€ and 512€ in 2010 [60]. The average yearly cost is therefore undoubtedly higher than for some other primary care drugs (e.g. thiazide diuretics) but when comparing the total drug expenditures, the latest French National Health Insurance report showed that hypertensives expenses amount to more than twice those incurred with lipid-lowering therapy used for primary prevention (Fig. 4) [61].

The discrepancy between average drug cost and actual expenditure is multifactorial:

- a combination of anti-hypertensives is often required to control HBP;
- there is a substantial rate of overtreatment with anti-hypertensives, and;
- evidence-based classes, such as diuretics, are not considered as first-line therapy [62].

Regarding statin-based therapy, it is also clear that the same inappropriate practices would also compromise the cost-effectiveness of primary prevention. Efforts should still be made to both avoid underuse and overuse of statins. In the UK, a recent large cohort study showed that there was a substantial proportion of overuse in low-CVD risk patients and underuse in high CVD risk patients, with large variations between general practices ranging from 8.2% to 61.5% statin use in high-risk patients and from 2.1% to 29.1% in low-risk patients [63].

These misuses were shown to offset the cost-effectiveness of statin-based primary prevention. Greving et al. [64] showed in a pharmaco-economic model that the cost-effectiveness of statins was not only related to drug cost, but also to variables, such as non-adherence rates and the “time horizon” (the time after which the evaluation is done). Basically, the higher the risk, the better the adherence and the longer the observation period (lifelong time horizon), the lower the cost-effectiveness would be (Fig. 5). By comparison, primary prevention would not be cost-effective in low-risk cardiovascular patients despite lowering generic statin costs.

The model was also sensitive to the projected efficacy of statins in a real-life setting. We showed in a recently published large case-control study that the magnitude of reduction of non-fatal ACS for statins observed in real-world French practice was similar to that found in RCTs [65]. After adjusting for baseline risk factors, prior exposure to statin therapy was significantly associated with an approximately 30% (27–33%) RRR for a first non-fatal ACS compared with non-users; this compared favourably with the 33% RRR in non-fatal CHD observed in the 2013 Cochrane meta-analysis discussed earlier. Importantly, consistent with the pharmaco-economic modelling by Greving et al., we found that targeting the highest risk group for a longer total statin exposure would be the most clinically effective, and thus, cost-effective, strategy (Table 2) [65].

Apart from the objective barriers to the implementation of primary prevention (clinical evidence, pharmaco-economic constraints), some subjective components should

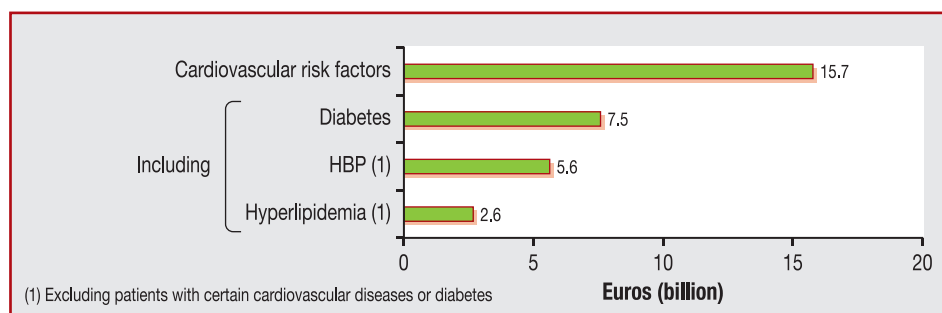


Figure 4. Expenditures associated with diabetes, arterial hypertension and hypercholesterolaemia (2011). HBP: high blood pressure. Data taken from [61].



Figure 5. Sensitivity analysis: cost-effectiveness results for different risk and time horizons. ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years (calculated by multiplying the time a person remained in a certain health state by the utility associated with that particular health state and subsequent summing up over all health states). *The 10-year vascular risk of fatal and non-fatal myocardial infarction and stroke was estimated from the expected number of first vascular events over the first 10 years divided by the total number of simulated people. Annual baseline incidence rates of initial vascular events by age group and sex were obtained from a record linkage study of Dutch nationwide registers. Different levels of 10-year risk of vascular disease were examined, from 1% to 30%. Reproduced with permission from [64].

be highlighted. We showed in France that there were marked differences between physicians' and patients' beliefs regarding the risk of hypercholesterolaemia, which subsequently induced a blurred perception of the disease [66], and it was demonstrated by an Italian group that physicians' beliefs were independently correlated with lipoprotein-lowering therapy prescription rate and hypercholesterolaemia control over a 3-year period in high-risk diabetic patients [67]. Thus, we should also take into account these subjective variables in our educational and awareness programmes, to appropriately implement primary prevention in high-risk patients. This approach is also essential to improve patient adherence to statins, which is a key determinant associated with the effectiveness of all pharmacological therapies.

Retrospective database analyses have revealed that 50% of patients receiving statins discontinue therapy after 1 year of treatment [68]. Studies also suggest that patient adherence to statin therapy is suboptimal, ranging from 30% to 70% in treated patients, and that persistence among those newly prescribed statins is low [69–71]. Poor adherence to statin therapy is associated with adverse health outcomes, including higher hospitalization rates and increased non-pharmacy medical costs [72–74].

Some studies have investigated data from various publications, analysing the sociodemographic, medical history and health care utilization variables reliably associated with statin non-adherence [68,75]. They identified a broad range of possible predictors, such as demographics, physician factors, health beliefs of patients, complexity of medication

Table 2 Assessment of the association between statin use and occurrence of first acute coronary syndrome, stratified by duration of current statin use and risk score, data from [65].

	ACS cases (n = 2234)	No ACS controls (n = 2236)	Crude matched OR (95% CI)	Adjusted matched ^a OR (95% CI)
Duration of current statin use				
≤ 1 year	68 (3.0)	73 (3.3)	0.86 (0.61–1.20)	0.82 (0.56–1.19)
> 1 to < 4 years	212 (9.5)	275 (12.3)	0.70 (0.58–0.86)	0.64 (0.51–0.79)
≥ 4 years	133 (6.0)	191 (8.5)	0.64 (0.51–0.81)	0.63 (0.49–0.82)
Statin use in 24 months				
Low-risk quartile ^b	65 (20.6)	186 (23.1)	0.81 (0.59–1.12)	0.83 (0.60–1.16)
Quartile 2 ^b	98 (21.5)	157 (25.9)	0.68 (0.50–0.93)	0.73 (0.53–1.00)
Quartile 3 ^b	137 (22.2)	149 (28.5)	0.66 (0.50–0.88)	0.70 (0.53–0.94)
High-risk quartile ^b	183 (21.6)	92 (30.5)	0.55 (0.40–0.75)	0.60 (0.43–0.83)

Data are number exposed (%), unless otherwise indicated. ACS: acute coronary syndrome; CI: confidence interval; OR: odds ratio.

^a Obtained by multiple conditional logistic regression, including smoking, hypertension, body mass index, physical activity, diabetes mellitus and alcohol consumption; matching variables were sex, age, number of visits to a general practitioner in the year preceding the index date, date of consultation and personal history of non-cardiovascular chronic disease.

^b Score risk obtained by multiple regression analyses, including body mass index, physical activity, smoking habits, alcohol consumption, hypertension, diabetes, hypercholesterolaemia and geographical origin of patients.

regimen, severity of disease, medication side effects and systemic barriers, which are probably not unique to statins and may represent a core set of easily obtainable variables that should be used to identify individuals and populations at risk of poor adherence to other cardiovascular medications (anti-hypertensives, aspirin, anti-diabetics). In the selected studies, adherence to statin therapy was measured using either a validated self-report scale or objective measures of adherence, including medication refill data, pill counts or electronic medication monitoring. Few studies assessed patients' perceptions of statin therapy with respect to non-adherence [76,77]. Interestingly, the three most commonly cited reasons for primary non-adherence were general concerns about the medication, a preference for lifestyle modifications [78] and fear of side effects. Particular attention should be paid to younger individuals and those who are taking statins as part of primary prevention, as these groups had the highest rates of non-adherence [75].

As reasons for primary non-adherence to statin therapy are multifactorial, individualized interventions may be warranted to improve adherence to statin therapy. It may be also helpful to institute interventions at the time of the initial prescription in particular. Gaining a better understanding of the range of underlying motivations for discontinuing therapy is critical for designing effective interventions. Identifying the types and sources of information patients use to learn about statins and their perceptions of cardiovascular risk factors could also improve clinician–patient communication about statins.

Conclusion

Hypercholesterolaemia is a well-known cardiovascular risk factor, which is asymptomatic compared with HBP or diabetes. Although lifestyle interventions, such as smoking cessation, weight loss and physical activities, are the first

therapeutic approach during primary prevention, a pharmacological intervention should be set up in patients at high cardiovascular risk. To date, there is sufficient proof coming from RCTs to remove all barriers to the prescription of effective therapeutic measures, including the administration of statins. Side effects are rare and most are not serious. The threshold of prescription is actually related to the countries' incomes. Compliance is a major problem in the success of primary prevention. All elements that affect compliance, linked either to the patients or to the media environment, have serious consequences for public health. Providing transparent and objective awareness should stimulate interest in following therapeutic guidelines based on all available evidence.

Disclosure of interest

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References

- [1] Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2095–128.

- [2] Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation* 2013;127:e6–245.
- [3] Nichols M, Townsend N, Scarborough P, et al. Cardiovascular disease in Europe: epidemiological update. *Eur Heart J* 2013;34:3028–34.
- [4] Lazo M, Hernaez R, Eberhardt MS, et al. Prevalence of non-alcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Epidemiol* 2013;178:38–45.
- [5] Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA* 2010;303:2043–50.
- [6] Gu Q, Burt VL, Dillon CF, et al. Trends in anti-hypertensive medication use and blood pressure control among United States adults with hypertension: the National Health And Nutrition Examination Survey, 2001 to 2010. *Circulation* 2012;126:2105–14.
- [7] Vervueren PL, Elbaz M, Dallongeville J, et al. Relationships between chronic use of statin therapy, presentation of acute coronary syndromes and one-year mortality after an incident acute coronary event. *Int J Cardiol* 2013;163:102–4.
- [8] Kuznik A, Mardekian J. Trends in utilization of lipid- and blood pressure-lowering agents and goal attainment among the US diabetic population, 1999–2008. *Cardiovasc Diabetol* 2011;10:31.
- [9] Kuznik A, Mardekian J, Tarasenko L. Evaluation of cardiovascular disease burden and therapeutic goal attainment in US adults with chronic kidney disease: an analysis of national health and nutritional examination survey data, 2001–2010. *BMC Nephrol* 2013;14:132.
- [10] Eliasson M, Janlert U, Jansson JH, et al. Time trends in population cholesterol levels 1986–2004: influence of lipid-lowering drugs, obesity, smoking and educational level. The northern Sweden MONICA study. *J Intern Med* 2006;260:551–9.
- [11] Ferrières J, Bongard V, Dallongeville J, et al. Trends in plasma lipids, lipoproteins and dyslipidaemias in French adults, 1996–2007. *Arch Cardiovasc Dis* 2009;102:293–301.
- [12] Grau M, Subirana I, Elosua R, et al. Trends in cardiovascular risk factor prevalence (1995–2000–2005) in northeastern Spain. *Eur J Cardiovasc Prev Rehabil* 2007;14:653–9.
- [13] Bongard V, Dallongeville J, Arveiler D, et al. Attainment of low-density lipoprotein cholesterol target in the French general population according to levels of cardiovascular risk: Insights from the MONA LISA study. *Arch Cardiovasc Dis* 2013;106:93–102.
- [14] Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011;32:1769–818.
- [15] Ferrières J, Amber V, Crisan O, et al. Total lipid management and cardiovascular disease in the dyslipidemia international study. *Cardiology* 2013;125:154–63.
- [16] Gitt AK, Drexel H, Feely J, et al. Persistent lipid abnormalities in statin-treated patients and predictors of LDL-cholesterol goal achievement in clinical practice in Europe and Canada. *Eur J Prev Cardiol* 2012;19:221–30.
- [17] Ferrières J, Berard E, Crisan O, et al. Residual dyslipidaemia after statin treatment in France: prevalence and risk distribution. *Arch Cardiovasc Dis* 2010;103:302–9.
- [18] Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol* 2012;60:2631–9.
- [19] Pletcher MJ, Bibbins-Domingo K, Liu K, et al. Nonoptimal lipids commonly present in young adults and coronary calcium later in life: the CARDIA (Coronary Artery Risk Development in Young Adults) study. *Ann Intern Med* 2010;153:137–46.
- [20] Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013, <http://dx.doi.org/10.1161/01.cir.0000437738.63853.7a>.
- [21] Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013;1:CD004816.
- [22] The Cochrane Database of Systematic Reviews—Issue 4 2013. *J Evidence-Based Med* 2013;6:115–6.
- [23] World Health Organization. English/French list of 182 non-governmental organizations in official relations with WHO reflecting decisions of EB128; 2011. Available at: <http://www.who.int/civilsociety/documents/NGOs-in-Official-Relations-with-WHO-2011-16-Mar-2011.pdf>
- [24] Taylor F, Ward K, Moore TH, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2011:CD004816.
- [25] Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL-cholesterol with statin therapy in people at low-risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;380:581–90.
- [26] Taylor FC, Huffman M, Ebrahim S. Statin therapy for primary prevention of cardiovascular disease. *JAMA* 2013;310:2451–2.
- [27] Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;375:735–42.
- [28] Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008;371:117–25.
- [29] Naci H, Brugts J, Ades T. Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246,955 participants from 135 randomized, controlled trials. *Circ Cardiovasc Qual Outcomes* 2013;6:390–9.
- [30] Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006;114:2788–97.
- [31] Holbrook A, Wright M, Sung M, et al. Statin-associated rhabdomyolysis: is there a dose-response relationship? *Can J Cardiol* 2011;27:146–51.
- [32] Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc Drugs Ther* 2005;19:403–14.
- [33] Mancini GB, Baker S, Bergeron J, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: proceedings of a Canadian Working Group Consensus Conference. *Can J Cardiol* 2011;27:635–62.
- [34] Semple SJ. Statin therapy, myopathy and exercise—a case report. *Lipids Health Dis* 2012;11:40.
- [35] Parker BA, Augeri AL, Capizzi JA, et al. Effect of statins on creatine kinase levels before and after a marathon run. *Am J Cardiol* 2012;109:282–7.
- [36] Mohassel P, Mammen AL. Statin-associated autoimmune myopathy and anti-HMGCR autoantibodies. *Muscle Nerve* 2013;48:477–83.
- [37] Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585–90.
- [38] Hamann PD, Cooper RG, McHugh NJ, et al. Statin-induced necrotizing myositis—a discrete autoimmune entity within the “statin-induced myopathy spectrum”. *Autoimmun Rev* 2013;12:1177–81.

- [39] Lahaye C, Beaufrere AM, Boyer O, et al. Immune-mediated myopathy related to anti 3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies as an emerging cause of necrotizing myopathy induced by statins. *Joint Bone Spine* 2014;81(1):79–82.
- [40] Mangravite LM, Engelhardt BE, Medina MW, et al. A statin-dependent QTL for GATM expression is associated with statin-induced myopathy. *Nature* 2013;502:377–80.
- [41] Laufs U, Weintraub WS, Packard CJ. Beyond statins: what to expect from add-on lipid regulating therapy? *Eur Heart J* 2013;34:2660–5.
- [42] Cohen JC, Boerwinkle E, Mosley Jr TH, et al. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med* 2006;354:1264–72.
- [43] de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004;292:1307–16.
- [44] Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005;294:2437–45.
- [45] Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL-cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670–81.
- [46] Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid-lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–504.
- [47] LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid-lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425–35.
- [48] Nemerovski CW, Salinitri FD, Morbitzer KA, et al. Aspirin for primary prevention of cardiovascular disease events. *Pharmacotherapy* 2012;32:1020–35.
- [49] Manes C, Giacci L, Sciartilli A, et al. Aspirin overprescription in primary cardiovascular prevention. *Thromb Res* 2006;118:471–7.
- [50] Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care* 2007;30:162–72.
- [51] Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;337:a1840.
- [52] Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008;300:2134–41.
- [53] Seshasai SR, Wijesuriya S, Sivakumaran R, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. *Arch Intern Med* 2012;172:209–16.
- [54] Messerli FH, Bangalore S, Julius S. Risk/benefit assessment of beta-blockers and diuretics precludes their use for first-line therapy in hypertension. *Circulation* 2008;117:2706–15, discussion 15.
- [55] Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various anti-hypertensive therapies used as first-line agents: a network meta-analysis. *JAMA* 2003;289:2534–44.
- [56] Wiysonge CS, Bradley HA, Volmink J, et al. Beta-blockers for hypertension. *Cochrane Database Syst Rev* 2012;11:CD002003.
- [57] Mora S, Glynn RJ, Hsia J, et al. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. *Circulation* 2010;121:1069–77.
- [58] Ridker PM. The JUPITER trial: results, controversies, and implications for prevention. *Circ Cardiovasc Qual Outcomes* 2009;2:279–85.
- [59] Reiner Z. Statins in the primary prevention of cardiovascular disease. *Nat Rev Cardiol* 2013;10:453–64.
- [60] Haute Autorité de santé. Annexes. Efficacité et efficience des hypolipémiants: une analyse centrée sur les statines; 2010. Available at: http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-07/annexes_efficacite_et_efficience_des_hypolipemiants_-_une_analyse_centree_sur_les_statines.pdf
- [61] Améliorer la qualité du système de santé et maîtriser les dépenses: propositions de l'Assurance maladie pour 2014 Rapport au ministre chargé de la sécurité sociale et au Parlement sur l'évolution des charges et des produits de l'Assurance maladie au titre de 2014 (loi du 13 août 2004); 2014. Available at: http://www.apmnews.com/documents/110713_pt.III.C.amp_P.pdf
- [62] Haute Autorité de santé. Évaluation des technologies de santé: analyse médico-économique. Évaluation par classe des médicaments antihypertenseurs; 2013. Available at: http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-05/rapport_evaluation_medicaments_antihypertenseurs.pdf
- [63] van Staa TP, Smeeth L, Ng ES, et al. The efficiency of cardiovascular risk assessment: do the right patients get statin treatment? *Heart* 2013;99:1597–602.
- [64] Greving JP, Visseren FL, de Wit GA, et al. Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis. *BMJ* 2011;342:d1672.
- [65] Grimaldi-Bensouda L, Rossignol M, Danchin N, et al. Real-life effectiveness of statins in the prevention of first acute coronary syndrome in France: a prospective observational study. *Int J Cardiol* 2013;169:271–5.
- [66] Durack-Bown I, Giral P, d'Ivernois JF, et al. Patients' and physicians' perceptions and experience of hypercholesterolaemia: a qualitative study. *Br J Gen Pract* 2003;53:851–7.
- [67] Franciosi M, Pellegrini F, De Berardis G, et al. Impact of physicians' beliefs and practices on cholesterol levels in patients with type 2 diabetes: a longitudinal assessment. *Am Heart J* 2005;149:104–11.
- [68] McGinnis B, Olson KL, Magid D, et al. Factors related to adherence to statin therapy. *Ann Pharmacother* 2007;41:1805–11.
- [69] Ellis JJ, Erickson SR, Stevenson JG, et al. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. *J Gen Intern Med* 2004;19:638–45.
- [70] Huser MA, Evans TS, Berger V. Medication adherence trends with statins. *Adv Ther* 2005;22:163–71.
- [71] International Society for Pharmaco-economics Outcomes Research. ISPOR Medication Compliance and Persistence Special Interest Group; 2008. Available at: <http://www.ispor.org/sigs/medication.asp> [accessed date: 15 May 2008].
- [72] Blackburn DF, Dobson RT, Blackburn JL, et al. Cardiovascular morbidity associated with non-adherence to statin therapy. *Pharmacotherapy* 2005;25:1035–43.
- [73] Degli Esposti L, Saragoni S, Batacchi P, et al. Adherence to statin treatment and health outcomes in an Italian cohort of newly treated patients: results from an administrative database analysis. *Clin Ther* 2012;34:190–9.
- [74] Wei L, MacDonald TM, Watson AD, et al. Effectiveness of two statin prescribing strategies with respect to adherence and cardiovascular outcomes: observational study. *Pharmacoepidemiol Drug Saf* 2007;16:385–92.

- [75] Mann DM, Woodward M, Muntner P, et al. Predictors of non-adherence to statins: a systematic review and meta-analysis. *Ann Pharmacother* 2010;44:1410–21.
- [76] Fung V, Sinclair F, Wang H, et al. Patients' perspectives on non-adherence to statin therapy: a focus-group study. *Perm J* 2010;14:4–10.
- [77] Mann DM, Allegrante JP, Natarajan S, et al. Predictors of adherence to statins for primary prevention. *Cardiovasc Drugs Ther* 2007;21:311–6.
- [78] Harrison TN, Derosé SF, Cheetham TC, et al. Primary non-adherence to statin therapy: patients' perceptions. *Am J Manag Care* 2013;19:e133–9.